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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,554	06/28/2001	Anna Edman Orlefors	HO-P0221US0	4792

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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,554	ORLEFORS ET AL.	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,27-31,39,40,46,47,50-53,61-71 and 73-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19, 27-31, 39-40, 46-47, 50-53, 61-71 and 73-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 11/7/2005 have been entered.

Claims 2, 4, 6, 12, 16, 20-26, 32-38, 41-45, 48-49, 54-60 and 72 have been cancelled. Claims 19, 46, 47, 51, and 61-67 have been amended and claims new claims 73-81 have been added. Claims 19, 27-31, 39-40, 46-47, 50-53, 61-71 and 73-81 are now pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. All rejections not reiterated herein are hereby withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS

Response to Arguments

Applicant's arguments with respect to claims 19, 27-31, 39-40, 46-47, 50-53, 61-71 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 19, 27-31, 39-40, 46-47, 50-53, 61-71 and new claims 73-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996) in view of Mian et al.(US Patent 6,319,469 B1).

Interpreting claim 19's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device(for example the capillary embodiment on page 88 bottom right).

With respect to claim 19, Ronaghi et al. teach a method of identifying a sequence of a portion of sample DNA comprising a microchannel structure in which there is a reaction chamber, wherein said method comprises the sequential steps of:

(i) attaching at least one primer DNA to between two and 100,000 reaction areas within the reaction chamber(Pg. 85, bottom right). Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) adding reagents including deoxynucleotide or deoxynucleotide analogue and DNA polymerase and moving said reagents within said microchannel structure to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide or deoxynucleotide analogue with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85- 86) and hybridizing the sample DNA in single stranded form to the primer DNA;

(iii) detecting whether or not the deoxynucleotide or deoxynucleotide analogue added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).

(iv) removing excess of said deoxynucleotide or deoxynucleotide analogue from said from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are immobilized, the reference further teaches the loss of these excess, unincorporated, deoxynucleotides following the wash steps on page 87.

(v) repeating sequentially steps (ii)-(iv) with different deoxynucleotides or deoxynucleotide analogues is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".

(vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the obtained sequence was confirmed by semi automated solid-phase Sanger sequencing"(Pg. 87, see figure 5).

With regard to applicant's limitation in claim 19, requiring the steps to take place sequentially, such a limitation, after further review, is seen as being taught by Ronaghi. Specifically the reference's FIG.1 depicts such a sequential method consisting of the addition of dXTPs, detection, and then washing, followed by the repetition of the cycle again.

With regard to claims 27, 29, 30, 68, 70, and new claims 74, 76 and 77, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85) which therein also teaches a fluorescent label.

With regard to claims 28, 69, 71, and new claim 75 Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

With regard to claims 39, 40, and new claims 79 and 80 the reference anticipates the limitations of the method of claims 39, 40, 79 and 80 wherein the amount of DNA sample is in the range of about 1 femtomole to about 200 pmole and also about 0.1 pmol to about 200pmol in their teaching on page 85 of "one picomole of the immobilized DNA fragment" being used in the sequencing reaction.

With regard to claims 50 and 52 the reference anticipates the limitations wherein said immobilized DNA is immobilized to a bead in their teaching on page 85 of "the biotinylated PCR products were immobilized onto streptavidin-coated super paramagnetic beads Dynabeads M280-Streptavidin or M450-streptavidin"(left hand side), which were later used for sequencing.

With regard to claim 53, the reference anticipates the limitation of where a DNA molecule destined for immobilization is formed outside the microfluidic device.

With regard to claims 61-67 and new claim 81, the microchannel structure comprises an application area that is common for more than one microchannel structure of the device wherein the microchannel structure is being interpreted as being a capillary tube or a reaction tube, and further wherein the common application area is being interpreted as an area where reagents are applied in common. In this case, such a limitation is met by either the opening of the capillary

tube or the opening of the reaction tube, both meeting the limitations of the claim as different dNTPs are added successively through these two common application areas which are also annular.

With regard to claim's 19, 46, 47, 51, 61, 66, new claims 73 and 81 and applicant's newly added limitation to the claims requiring attaching at least one primer DNA to between two and 100,000 reaction areas within the reaction chamber, a microfluidic device comprising more than one microchannel structure having an application area that is common for said more than one microchannel structure and each microchannel structure has a reaction chamber are also seen as being taught by Ronaghi. Specifically, Ronaghi teach on page 85 left hand side that the "oligonucleotide E3PN and the above described PCR product were used as templates for real-time DNA sequencing and the oligonucleotide E3PN was immobilized onto streptavidin-coated super paramagnetic beads". Thus the oligo was immobilized to two or more reaction areas since the entire bead was used, and not only a single oligo was immobilized on a single bead, many on multiple locations were affixed. Also, it is important to note that the office's interpretation of reaction area is due in part to the fact that the beads(presently viewed as "reaction areas"), are incubated with T7 DNA polymerase, and as a result subjected to an extension reaction of the polymerase.

But, with respect to Claims 19, 31, 46, 47, 51, 53, and new claims 73 and 78 Ronaghi et al. does not teach a method for identifying the sequence of a portion of sample DNA wherein the steps are performed in a microfluidic device that is a disk and the fluids are moved(claims 19, 31, 46, 47, 51, and new claims 73 and 78) by centripetal force, such as that which is referred to on page 5, line 32 of the current specification. Additionally, they do not teach the microfluidic

device comprising microchannel structures with a common application area and a reaction chamber in each of said microchannel structures. Furthermore, Ronaghi et al. does not teach labeling the deoxynucleotide, deoxynucleotide analogue, or dideoxynucleotide that is added in the method.

However, Mian et al. (US Patent 6,319,469 B1) teach performing the previously taught methods of Ronaghi inside another type of microfluidic device. Mian et al. teach performing the steps of adding sample DNA on a reaction area in a microfluidic device(see Col. 49 lines 1-4), attaching or hybridizing single stranded DNA, and plainly adding sample DNA to a predetermined area on a microfluidic device that is a disc and whose fluids can be moved to various chambers(Col. 49 lines 2-19). Furthermore, the Mian et al. reference adds teachings of a disc-shaped, microfluidic device that causes fluid movement through the use of centripetal force(Col. 3 lines 5-25). The reference even further teaches that such methods and apparatus are advantageous as they fill the need in the art for a "simple, flexible, reliable, rapid, and economical microanalytic and microsynthetic reaction platform for performing biological, biochemical, and chemical analyses and syntheses that can move nanoliter to microliter amounts of fluids"(Col. 3 lines 5-10). The reference provides that the invention also advantageously combines "wet" chemistry capabilities with information processing, storing and manipulating ability. The addition of the disc-shaped microfluidic device that exploits centripetal force, to this method for sequence identification, conferred the ability to properly mix reaction components, remove reaction side products, and isolate desired reaction products and intermediates.(Col 3, lines 5-25)(Col 48, line 67) Furthermore, Mian et al. add the teaching of forming DNA to a "microchannel structure" within the microfluidic device. The reference teaches that; the unique

disc shape and ability to move nanoliter to microliter amounts of fluid, including reagents and reactants, at rapid rates to effect the proper mixing of reaction components through the use of microchannel structures and centripetal force, provides a remedy for the many deficiencies of the status quo. The use of microchannels, functioning to separate micro-amounts of fluid reagents, and centripetal force, to move fluids into and out of reaction chambers, facilitates high-throughput analysis for both genome sequencing and routine clinical applications "that are sophisticated(for professional, eg hospital, use), easy to use(for consumer eg at-home monitoring, uses), and portable (for field environmental testing, use)" (Col. 3 lines 19-22). In addition, with regard to the new limitations requiring multiple reaction(at least two, different) areas containing immobilized DNA(i.e. amended claims 46, 48, 49, 54, and 56) Mian et al. teach "disks comprising a multiplicity of these synthetic arrays, permitting simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides"(Col. 49 lines 31-34). Applicant's newest amendments are not interpreted as changing the sense of the previously presented claims. Furthermore, with regard to claim 53 and its limitation requiring that the immobilized DNA is formed outside the microfluidic structure(i.e. claim 53) Mian et al. teaches in Col.42 lines 64-67 for example, that "in the practice of the method of the invention, the immobilized, labeled duplex is placed on the disk and subjected to a flow stream of a buffered solution contained on the disk"(Col. 42) also in Col. 43 lines 26-33 the reference teaches immobilization of DNA either before or after the DNA is on the disk.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. by incorporating a disc-shaped microfluidic device with microchannels and caused

fluid flow through the use of centripetal force in order to have achieved the expected benefit of providing a method that could be used for the automation of larger sequencing projects and for the provision of a "high-throughput system."

With respect to Claims 29and 30, and new claims 76 and 77 and the limitation of a fluorescently labeled dideoxynucleotide, Mian teaches a detection step that involves a labeled terminator (Col 49, lines 5-10). Mian et al. teach a method wherein the detection step comprises the DNA being transferred into a mixing chamber containing terminator solution by spinning the disk(Col. 47 lines 15, 28, 39 for example). Terminator solution typically comprises 100nl of a solution containing 5 picomoles of each deoxynucleotide and 0.5 picomoles of one dideoxynucleotide covalently linked to a fluorescent label. The set of dideoxynucleotide-terminated DNA fragments comprising the reaction mixture is then separated by capillary electrophoresis and the sequence of the fragments determined by laser-induced fluorescence detection. The reference further teaches that this mode of detection ie, discs comprising a multiplicity of these synthetic arrays with fluorescent labels, permits the simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches. Mian et al. teaches the use of a terminator solution containing a dideoxynucleotide covalently-linked to a fluorescent label in Example 7, Col. 49. In addition, Mian et al. teach, in addition to the aforementioned, fluorescently labeled dideoxynucleotide of Example 7, Example 3 which includes the incorporation of fluorescently labeled DNA to one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. and to have added a labeled terminator and fluorescently labeled dideoxynucleotides, in order to have achieved the benefit of providing a method that, would permit the simultaneous synthesis of a plurality of fluorescently labeled dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/20/2006

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